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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,726	11/14/2001	Avi J. Ashkenazi	P2730P1C16	3311

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,726	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 120-123 are pending and under consideration.

This Office Action is in response to applicant's amendment filed 11/4/2004.

The new title of the invention is acknowledged.

The rejection of claims 119-124 under 35 U.S.C. §112, second paragraph is withdrawn in view of applicant's amendments.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 122-126 and 129-131 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility for reasons cited in the previous Office Action mailed 6/3/2004, at pages 3-5. Applicant argument, filed 11/4/2004 has been fully considered, but is not deemed persuasive, for reasons below:

At pages 6-7 of the response, applicants review the standards for utility under 35 U.S.C. §101. Applicants argument that the Examiner has failed to assert a *prima facie* case of lack of utility is not persuasive; see pages 3-5 of the previous office action. The Examiner maintains that a prima facie case of lack of enablement has been established in the previous Office Action. While absolute predictability is not a requirement for utility, the Examiner has established that the skilled artisan would not consider the meager amount of amplification of the nucleic acid encoding the claimed polypeptides in a minor fraction of assayed tissues to be predictive of over expression of the claimed polypeptide in a manner that would allow diagnostic use of such.

Bridging pages 7-8, applicants argue that the amplification of the nucleic acid encoding the claimed polypeptide is significant, and cite a declaration by Dr. Goddard. This argument has been fully considered but is not deemed persuasive because the 2-3 fold amplification of the nucleic acid is not predictive of protein levels.

The declaration under 37 C.F.R. §1.132 by Dr. Goddard has been fully considered. The Goddard declaration is not pertinent, as it is drawn to the significance of the amplification of the nucleic acids, and fails to address the issue of the claimed protein.

At page 8, applicants argue that both the Examiner and Sen teach that aneuploid tissues are cancerous of pre-cancerous. This argument has been fully considered but is not deemed persuasive. Applicants statement is erroneous. Sen includes no teaching that all aneuploid tissues are cancerous or pre-cancerous, nor did the Examiner make any such statement. Rather, both Sen and the Examiner state that cancerous tissues are known to be aneuploid. It is also true that pre-cancerous tissues *may* be aneuploid. The converse is *not* true. Aneuploidy is also a feature of damaged tissue, and is commonly found in colon and lung tissues, which are subject to environmental damage. It does not invariably lead to cancer. Further, it remains that the 2-3 fold amplification of the nucleic acid is not predictive of a similar differential in protein expression; hence, the argument is not persuasive, as the claims are drawn to antibodies that bind to polypeptides, not the nucleic acids that encode the polypeptides.

Applicants argue that the declaration by Dr. Ashkenazi establishes the significance of amplification of nucleic acids. The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene *products* (such as the polypeptide to which the claimed antibodies bind) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Applicants argument of the Pennica reference at page 8 of the response has been fully considered but is not deemed persuasive. Applicants have plucked a single phrase from the portion cited by the Examiner, which phrase supports their assertion of utility. However, they have taken that phrase out of context; the teachings of Pennica as a whole support the opposite conclusion, that utility of the polypeptide cannot be predicted based upon amplification of the nucleic acid, for reasons set forth at page 5 of the previous office action.

Applicants argument at pages 9-10 that there is expected to be a correlation between gene amplification and protein overexpression, with reference to an article by Ornfoft et al., has been fully considered but is not deemed persuasive. Ornfoft et al. *could only compare the levels of about 40 well-resolved and focused abundant proteins."* (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Ornfoft publication, and an associated rise in level of the encoded protein. The Hyman reference cited by applicants found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of SEQ ID NO: 222 would be correlated with elevated levels of mRNA. Further, Hyman does not examine protein expression. Applicants are reminded that the instant claims are directed to proteins. Similarly, Pollack, cited by applicants, does not analyze protein levels, nor does Pollack support the assertion that it is predictable, on the basis of the minimal increase in copy number of SEQ ID NO: 222 that the protein would accordingly be found at altered levels. Accordingly, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed protein. The art, taken as a whole, clearly teaches that it is not predictable that a two-fold copy

increase in the nucleic acid would translate to detectable over-expression of the associated mRNA, much less any protein encoded thereby. Further, as evidenced by the Orntoft publication, the type of data presented in the instant specification clearly does not meet the standard in the art for establishing association of a protein with cancer. Accordingly, the claimed antibodies have no real-world, readily available use.

At page 10, Applicant presents a discussion of the declaration by Dr. Polakis filed under 37 CFR 1.132 with the response. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1800 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 22-29, 35 and 37-41 based upon 35 U.S.C. §101 and §112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in

transcript expression levels between normal and cancerous tissue. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Accordingly, the claimed antibodies have no real-world, readily available use.

At page 11, applicants reiterate their discussion of the Ashkenazi declaration, which has already been discussed, above.

Applicants argue (page 12) that Hanna et al. teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-123 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record, and above.

Rejections over Prior Art

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 119 and 124 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 2001 42451-A1. See enclosed sequence alignment, which corresponds to claim 21, page 827-828 of WO document. According to the abstract therein, the disclosure also discloses production of antibodies to the proteins.

Applicants argument at page 13 of the response that the reference does not apply as prior art has been fully considered but is not deemed persuasive. As the claims remain under a rejection for lack of utility, priority is denied to parent applications, which were not in compliance with 35 U.S.C. §101.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119, 120, 123 and 124 remain rejected under 35 U.S.C. 103(a) as being unpatentable over clone H74302, isolated by L. Hillier et al., WashUMerck EST Project 1995 in view of Sibson et al., WO94/01548.

Applicants argument at page 13 of the response has been fully considered but is not deemed persuasive. The specification clearly states that the clone was purchased from Merck, and sequenced to obtain the sequence identified as PRO809. Applicants allegation to the contrary, in the absence of evidence, is not persuasive. In order to overcome this rejection, applicants must submit evidence in appropriate form as to what the actual sequence of the clone was, including an alignment to the claimed nucleic acids, in order for the Examiner to make a factual determination contrary to the admissions in the specification.

Claims 120, 123 and 124 are rejected under 35 U.S.C. 102(b) as being anticipated by L. Hillier et al., WashUMerck EST Project 1995 in view of Sibson, for reasons of record in the previous Office Action.

Applicants argument that the antibodies found obvious over the prior art do not meet all the limitations of the claims has been fully considered but is not deemed persuasive. The claims are drawn to antibodies that "specifically" bind to the protein of

SEQ ID NO: 223. As used in the art, 'specific' is not necessarily synonymous with 'binds exclusively to' as implicitly urged by applicants. Rather, specificity is relative, such that antibodies 'specific' for one protein can bind to another protein with similar sequence. For example, antibodies specific to PDGF have, indeed, been described as binding to CTGF, as evidenced by U.S. Patent Number 5,783,187. Accordingly, antibodies to the prior art proteins that also bind to the same epitopic structure of SEQ ID NO: 223 would be considered to be "specific. Thus, the prior art fairly makes obvious antibodies that would bind the protein of SEQ ID NO: 223.

Claims 121 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillier et al., any one of loci H74302, H74303 H73373 H58326 or RO2548, any one in view of Sibson as cited in the above rejections under 35 U.S.C. § 103(a), and further in view of U.S. Patent Number 5,565,332 (Hoogenboom et al.) in the case of claim 121, or in view of U.S. Patent Number 4,946,778 (Ladner et al.) in the case of claim 122 for reasons of record in the previous Office Action.

Applicants argument of this rejection has been fully addressed above.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner

2/19/2005